SB-271046 SmithKline Beecham

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SmithKline Beecham is developing the 5-HT$_6$ antagonist, SB-271046, as a potential cognition enhancer. By December 1999, phase I trials had commenced [360354]. This drug was originally being developed primarily for the treatment of schizophrenia [284490], however, cognitive disorders, including but not limited to Alzheimer's disease, have been the main target since 1998 [394309].

SB-271046 is a potent, selective 5-HT$_6$ antagonist with a pK$_i$ value of 8.9 [333710].

SB-258585, also known as 4-iodo-N-[4-methoxy-3-(4-methyl-piperazin-1-yl)phenyl]benzenesulfonamide is an analog of SB-271046 [322488].

Data recently presented at the Society for Neuroscience annual meeting in November 2000 demonstrated that administration of SB-271046 resulted in a significant increase in glutamate and aspartate levels in the frontal cortex, without affecting noradrenaline, dopamine or 5-HT levels. This was stated to suggest that 5-HT$_6$ antagonists might therefore be useful for treating cognitive dysfunction [390469]. The drug has also been radiolabeled in order to provide an assay for estimating in vivo 5-HT$_6$ receptor occupancy [390470].

Originator SmithKline Beecham plc

Status Phase I Clinical

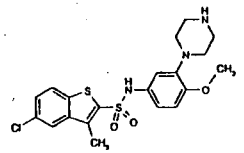
Indication Schizophrenia

Action 5-HT$_6$ antagonist

Synonyms SB-258585

CAS Benzo[b]thiophene-2-sulfonamide, 5-chloro-N-[4-methoxy-3-(1-piperazinyl)phenyl]-3-methyl-
Registry No: 209481-20-9
Note: SB-271046

CAS Benzenesulfonamide, 4-iodo-N-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-
Registry No: 209480-63-7
Note: SB-258585



Introduction

Since atypical antipsychotics, and some antidepressants, have relatively high affinities for certain subtypes of serotonin (5-HT) receptors, there has been an improved effort to find new compounds with high selectivity and affinity for these receptors. It is hoped that compounds discovered by such a strategy could be utilized in the treatment of psychiatric disorders [345797]. Amongst the numerous subtypes of 5-HT receptors, the 5-HT$_6$ subtype has recently attracted special attention, since some of the most effective antipsychotics (such as clozapine), and some antidepressants, demonstrate high affinity for this receptor subtype, where they act as antagonists [389841].

5-HT$_6$ receptors are present at high levels in key structures of the forebrain, such as the cortex, caudate/putamen, nucleus accumbens, and hippocampus [333710]. Moreover, a role for these receptors in memory and cognition was suggested when it was found that administration of antisense oligonucleotides directed to mRNA encoding the 5-HT$_6$ receptor induces a behavioral syndrome that is blocked by the muscarinic antagonist, atropine [389843]. Accordingly, it was suggested that 5-HT$_6$ receptor antagonists might be useful for the treatment of memory and cognitive dysfunction.

The first selective antagonists developed for the 5-HT$_6$ receptor were Ro-04-6790 and Ro-63-0563 (F Hoffman-La Roche Ltd), which both had moderate affinity for the receptor. As expected, they also appeared to enhance cholinergic neurotransmission [383182]. However, these compounds had poor brain penetration. Further development of selective antagonists led to SB-271046, which has both high affinity and high selectivity for 5-HT$_6$ receptors, high oral bioavailability and brain penetration compared with the early agents.

Synthesis and SAR

SB-271046, also known as 5-chloro-3-methyl-benzo[*b*]thiophene-2-sulphonic acid (4-methoxy-3-piperazin-1-yl-phenyl)amide monohydrochloride, was obtained after studies performed on a variety of compounds screened against cloned human 5-HT$_6$ receptors [315662]. One of these compounds, 4-bromo-N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]benzenesulfonamide, showed high affinity (pK$_i$ = 8.3) for the 5-HT$_6$ receptor and a 50-fold greater selectivity at a number of other receptors, including ten different 5-HT receptor subtypes. In order to study SAR related to SB-214111 (SmithKline Beecham plc), 4-methoxy-3-(4-methylpiperazin-1-yl)-aniline was coupled with various sulfonyl chlorides encompassing several different aromatic nuclei. Among them, the 5-chloro-3-methylbenzothiophene derivative was identified as the most potent (affinity pK$_i$ = 9.2) and selective compound (300-fold more selective for 5-HT$_6$ receptor than for 13 other receptor types). This compound was metabolically N-dealkylated in rats to produce a derivative which was found in blood at significant levels, and had a structure corresponding to that of SB-271046. Subsequently SB-271046 was synthesized via the BOC-protected piperazine.

Pharmacology

SB-271046 binds with great affinity to the serotonin 5-HT$_6$ receptor (pK$_i$ = 8.9 for human receptors; pK$_i$ = 9.3 for rat receptors) and showed good selectivity for this receptor (> 200-fold) compared to more than 54 receptors, enzymes and channels [334508]. In a functional adenylate cyclase assay with HeLa cell membranes [315662], SB-271046 was a competitive antagonist (pA2 = 8.7). The compound demonstrated no significant inhibition of the major human P450 enzymes *in vitro*. In the rat, pharmacokinetic studies showed that SB-271046 has a brain penetration of 10%, low blood clearance (7.7 ml/min/kg) and an oral bioavailability > 80% [315662]. In an *ex vivo* study with homogenates of brain striatum from rats treated *in vivo* with 0.1 to 100 mg/kg of SB-271046, binding of the specific, radiolabeled 5-HT$_6$ receptor ligand, [^{125}I]SB-258585, was prevented with ED$_{50}$ = 30 mg/kg [339415], [346161], [382544], [389849].

In vivo effects of SB-271046 on brain neurochemistry were recently studied by Dawson *et al* using microdialysis from the striatum and frontal cortex in the freely moving rat [378931]. SB-271046 (10 mg/kg) did not change the concentrations of 5-HT, dopamine or noradrenaline in any of the regions studied. Concentrations of aspartate and glutamate remained also unchanged in the striatum. However, SB-271046 produced increases in glutamate (> 3-fold) and aspartate (> 2- fold), as measured in the cortex. This effect was blocked by tetrodotoxin, a sodium channel blocker, suggesting that SB-271046 induces the release of glutamate and aspartate from a neuronal population in the cortex. As yet, there is no evidence to suggest an interaction of SB-271046 on glutamate transporters. Consequently, the authors of the study speculate that SB-271046 enhances excitatory neurotransmission by blocking tonic serotonergic inhibition of cortical excitatory afferents.

The localization of the 5-HT$_6$ receptors responsible for the actions of SB-271046 and its analogs is most likely post-synaptic, since autoradiography, immunohistochemical and mRNA *in situ* hybridization show that the receptor appears to be near to the site of protein synthesis (somata and dendrites) [379025], [389841]. In addition, dendritic localization of 5-HT$_6$ receptors in the striatum and dentate gyrus has been demonstrated in the rat [391679]. Since 5-HT$_6$ receptor mRNA has not yet been identified in the raphe, this suggests that 5-HT$_6$ receptors are not found presynaptically on serotonergic neurons but post-synaptically on target neurons, eg, in the striatum and dentate gyrus. It remains possible that 5-HT$_6$ receptors may be heteroreceptors on serotonergic terminals.

The expression level of the immediate early gene, c-fos, is affected by antipsychotics. One study compared the expression of Fos-like immunoreactivity after treatment with SB-271046, clozapine or haloperidol [379022]. Only haloperidol and clozapine produced a significant increase in Fos-like immunoreactive structures in the striatum, while SB-271046 did not produce any change. The reason for this lack of c-fos activation is unknown as it suggests that any putative antipsychotic or cognitive effects of SB-271046 do not involve changes in c-fos expression levels.

SB-271046 also presents anticonvulsant effects, as assessed in the rat maximal electroshock threshold test [322488], [378931]. SB-271046 produced an increase in seizure threshold over a range of doses (0.1 to 30 mg/kg po, 2 h before testing), with a minimal affective dose of 0.1 mg/kg. At 10 mg/kg, the effect was sustained up to 8 h. No evidence of tolerance to the anticonvulsant activities of SB-271046 was observed following repeated administration at 10 mg/kg bid for 7 days. No behavioral side effects were noticed. It was concluded that SB-271046 produced potent and long-lasting anticonvulsant activity, although the magnitude of this effect was modest in comparison to that of known anti-epileptic drugs, such as carbamazepine, evaluated in the same model [322488]. The level of anticonvulsant activity correlated with the concentration of SB-271046 in blood (EC$_{50}$ = 0.16 µM) and in brain (C$_{max}$ = 0.01 to 0.04 µM) [334513], [385302].

The cholinergic system plays fundamental roles in memory and cognitive functions. Accordingly, two studies to determine the effects of SB-271046 in two rat models of memory and learning were conducted [389855], [319557], [322488]. In the water maze spatial learning task, there was no significant effect of treatment on acquisition of the water maze. However, a repeated measures analysis showed a significant effect of treatment on the percentage of time spent in the platform quadrant and a significant difference between vehicle and 10-mg/kg groups. In a different experiment, using a T-maze spontaneous alternation task in aged rats, effects of SB-271046 on choice accuracy were investigated. At 20 mg/kg, SB-271046 attenuated the deficit in T-maze choice accuracy induced by a 30-s delay.

As discussed previously, the administration of antisense oligonucleotides directed to 5-HT$_6$ receptor mRNA induced a behavioral syndrome that could be blocked by atropine [389843]. In addition, Bourson *et al* reported that, in 6-hydroxydopamine lesioned rats, the 5-HT$_6$ receptor antagonist, Ro-04-6790 (F Hoffman-La Roche Ltd), inhibited rotational behavior induced by the muscarinic antagonists, scopolamine and atropine [391714].

Since 5-HT$_6$ receptor activation appears to regulate the cholinergic system, the effects of SB-271046 on yawning were investigated in rats [334508]. This compound had no effect on yawning *per se*. However, SB-271046 (10 mg/kg po) enhanced the increased yawning produced by physostigmine (0.3 mg/kg ip).

Metabolism

SB-271046 demonstrated no significant inhibitory activity at the major human P450 enzymes *in vitro*. In the rat, pharmacokinetic studies showed that SB-271046 has a brain penetration of 10%, low blood clearance (7.7 ml/min/kg) and an oral bioavailability > 80% [315662].

Toxicity

No toxic effects have been described to date in the animal tests performed with SB-271046. In a rat maximal electroshock seizure threshold test of the anticonvulsant properties of SB-271046, no behavioral depressant action was observed [334513].

Clinical Development

Phase I

Trials in volunteers had started by December 1999, but no data are currently available [360354].

Side Effects and Contraindications

No data are currently available.

Current Opinion

In animal models, SB-271046 demonstrates specific cognitive effects. These effects appear to be mediated by 5-HT$_6$ receptor-induced changes in levels of glutamate and acetylcholine or in the responses of their receptors, while levels of dopamine, 5-HT and norepinephrine undergo little or no change. This specificity of action, without other apparent side or toxic effects, may prove very valuable for treating cognitive abnormalities in schizophrenia and neurodegenerative diseases. The specificity of action, however, would also predict that antagonists of 5-HT$_6$ receptors would have less effect on other aspects of the pathophysiology of schizophrenia or other cognitive disorders related to alterations in monoamines. However, given the complexity of human emotional and cognitive functions, only clinical trials with SB-271046 will provide the evidence necessary for understanding the influence of 5-HT$_6$ in the various higher functions of the human brain.

Development history

Developer	Country	Status	Indication	Date	Reference
SmithKline Beecham plc	UK	C1	Schizophrenia	27-MAR-00	360354

Literature classifications

Chemistry

Study Type	Result	Reference
Synthesis and SAR	SB-271046 is the N-demethylated form of the 5-chloro-3-methylbenzothiophene derivative of 4-bromo-*N*-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]enzenesulfonamide.	315662, 334508
SAR	Cis orientation of the aromatic rings around the sulfonamide is preferred.	338560
SAR	Sulfonamide linkage is better than an amide moiety.	338560
SAR	The piperazine ring interacts with an aspartic acid residue in transmembrane loop III of the 5-HT$_6$ receptor.	338560

Biology

Study Type	Effect Studied	Experimental Model	Result	Reference
In vitro	Receptor selectivity.	Radioligand binding assay.	The ^{125}I derivative of SB-258585 (4-[^{125}I]phenylsulfonyl analog of SB-271046) is highly selective for 5-HT$_6$ receptors.	315662
In vitro	Receptor binding properties.	Radioligand binding assay.	Radioactive analog, SB-258585, has high affinity for recombinant human 5-HT$_6$ receptor expressed in HeLa cell lines.	322488
In vitro	Localization of 5-HT$_6$ receptors.	Binding of radioactive analog, SB-258585, to brain sections.	High levels in the cerebral cortex, nucleus accumbens, caudate-putamen and CA1/dentate gyrus of the hippocampus, and at moderate levels in the substantia nigra and thalamus.	333710
In vivo	Yawning.	Physostigmine-induced (1, 3, 10 mg/kg po) yawning in rats.	Significant increase in induced yawning at 10 mg/kg.	322488, 334508
In vivo	Anticonvulsant activity.	Rat maximal electroshock seizure threshold test. Doses of 0.1 to 30 mg/kg.	Dose-dependent elevation of seizure threshold (MED = 0.1 mg/kg). At 10 mg/kg, effect was sustained up to 8 h.	334513, 385302
In vivo	c-Fos expression.	Administration of SB-271046, 10 mg/kg po.	No changes in c-Fos immunoreactivity.	379022
In vivo	Memory (retention).	The water maze test in rats.	Improved retention with 10 mg/kg dose.	389855
In vivo	Learning.	Operant delayed alternation task by aged rats.	Improvement in choice accuracy at 1 mg/kg.	389855
In vivo	Levels of serotonin (5-HT), dopamine (DA), noradrenaline (NA), glutamate (GL), and aspartate (AS).	Microdialysis of freely moving rats in striatum and frontal cortex.	No change in basal levels of 5-HT, NA or DA in any region. No change in GL or AS in striatum. Tetrodotoxin-dependent increase of GL (82.3%) and AS (62.1%) in frontal cortex.	378931
Ex vivo	Binding inhibition of SB-258585.	*Ex vivo* binding assay.	SB-271046 and SB-214111 inhibited the binding of SB-258585 with ED_{50} = 30 mg/kg.	382544

Metabolism

Study Type	Effect Studied	Experimental Model	Result	Reference
In vivo	Oral bioavailability.	Oral administration in rats.	Oral bioavailability > 80%.	315662
In vivo	Half life.	Oral administration in rats.	$T_{1/2}$ = 4.8 h.	315662
In vivo	pA2.	Oral administration in rats.	pA2 = 8.7.	315662
In vivo	Brain penetration.	Oral administration in rats.	Moderate (10%).	315662
In vivo	Brain:blood ratio.	Oral administration in rats.	Ratio of 0.1.	338560
In vitro	Cytochrome P450 inhibition.	Human microsomal preparations.	No inhibition of cytochrome P450.	338560

Associated patent

Title Sulfonamide derivatives with 5-HT$_6$ antagonist activity for treating CNS disorders.

Assignee SmithKline Beecham plc

Publication WO-09827081 25-JUN-98

Priority GB00026377 19-Dec-96

Inventors Bromidge SM, King FD, Wyman PA.

Associated references

284490 SmithKline Beecham R&D review meeting, London, UK. Muhsin M *IDDB MEETING REPORT* 1998 April 16

315662 5-Chloro-N-(4-methoxy-3-piperazin-1-ylphenyl)-3-methyl-2-benzothiophenesulfonamide (SB-271046): a potent, selective and orally bioavailable 5-HT$_6$ receptor antagonist Bromidge SM, Brown AM, Clarke SE, Dodgson K, Gager T, Grassam HL, Jeffrey PM, Joiner GF, King FD, Middlemiss DN, Moss SF *et al J MED CHEM* 1999 42 2 202 - 205
•• *The 5-HT$_6$ receptor is a novel serpentine 5-HT receptor type, highly expressed in the CNS, which is positively coupled to adenylyl cyclase. It has been suggested as a potential target for the treatment of schizophrenia, depression and memory dysfunction. Few selective ligands have been reported and those that have, eg, Ro-63-0563 (F Hoffmann-La Roche), are poorly effective at crossing the blood-brain barrier. Novel, selective 5-HT$_6$ receptor antagonists are reported, which should help to clarify the physiological role of this 5-HT receptor type. This is an account of the development of SB-271046, its synthesis, structure activity relationships, affinity for 5-HT$_6$ receptors and some of its pharmacokinetic properties.*

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322488 Joint Meeting of The British and Portuguese Pharmacological Societies Casa Diocesana, Porto, Portugal McLean PG *IDDB MEETING REPORT* 1999 April 8-9

333710 British Pharmacological Society - Summer Meeting Nottingham, UK Chazot P *IDDB MEETING REPORT* 1999 July 14-16
• *Report of the autoradiographic localization of the 5-HT$_6$ receptor in the rat brain and its possible origin.*

334508 Characterization of SB-271046, a potent and selective 5-HT$_6$ receptor antagonist. Routledge C, Price GW, Bromidge SM, Moss SF, Newman H *BR J PHARMACOL* 1999 127 Proc Suppl 21P
• *Report on the affinity, inhibition of 5-HT-induced adenylate-cyclase activation and effects on yawning behavior for SB-271046.*

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• *Study of the binding properties of radiolabeled SB-258585, a radioactive analog of SB-271046, on human recombinant 5-HT$_6$ receptors.*

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•• *Review on the involvement of 5-HT receptors in the actions of antipsychotic drugs.*

346161 [^{125}I]SB-258585 - A selective antagonist radioligand for recombinant and native human 5-HT$_6$ receptors. *SOC NEUROSCI ABSTR* 1999 25 Part 1 Abs 485.12
•• *Study of the binding properties of radiolabeled SB-258585, a radioactive analog of SB-271046, on human recombinant 5-HT$_6$ receptors and in native human receptors from several brain areas.*

360354 SmithKline Beecham plc *ANNUAL REPORT* 1999 December 31

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•• *First account of the neurochemical effects of 5-HT$_6$ receptor antagonism in frontal cortex and striatum, using SB-271046.*

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•• *Report on the expression of the immediate early response gene c-fos in the rat brain after treatment with clozapine, haloperidol, or SB-271046.*

379025 Autoradiographic localisation of the 5-HT$_6$ receptor in the CNS of the rat using [^{125}I]SB-258585. Roberts JC, Hirst WD, Reavill C, Patel S, Routledge C, Leslie RA *BR J PHARMACOL* 1999 128 Proc Suppl 156P
• *Localization of 5-HT$_6$ receptors using SB-258585, an analog of SB-271046, in normal rat and in rats with 6-hydroxydopamine lesions of the median forebrain bundle.*

382544 British Pharmacological Society Meeting University of Bradford, UK Chazot P *IDDB MEETING REPORT* 2000 September 6-8

383182 Investigation of stretching behaviour induced by the selective 5-HT$_6$ receptor antagonist, Ro 04-6790, in rats. Bentley JC, Boursson A, Boess FG, Kone FC, Marsden CA, Petit N, Sleight AJ *BR J PHARMACOL* 1999 126 7 1537 - 1542
• *Study on the first selective antagonists for the 5-HT$_6$ receptors and their behavioral effects*

385302 Characterization of SB-271046 ; a potent, selective and orally active 5-HT$_6$ receptor antagonist. Routledge C, Bromidge SM, Moss SF, Price GW, Hirst W, Newman H, Riley G, Gager T, Stean T, Upton N, Clarke SE, Brown AM *BR J PHARMACOL* 2000 130 7 1606 - 1612
•• *Studies of the affinity and selectivity of SB-271046 for 5-HT$_6$ receptors, accompanied by determination of the antagonism of the 5-HT-induced activation of adenylate-cyclase and the anticonvulsant effects in the rat maximal electroshock seizure threshold.*

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•• *Behavioral effects of antisense oligonucleotides to down-regulate the expression of the 5-HT$_6$ receptor, and the antagonism of those responses with atropine*

389849 Ex vivo binding with [^{125}I]SB-258585; an assay to estimate *in vivo* 5-HT$_6$ receptor occupancy. Hirst WD *SOC NEUROSCI ABSTR* 2000 26 810 - 814
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** *SB-271046-induced enhancement of some memory functions observed in the water maze and the T-maze.*

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391714 Involvement of 5-HT$_2$ receptors in nigro-striatal function in rodents. Bourson A, Boess FG, Bös M, Sleight AJ. *BR J PHARMACOL* 1998 125 7 1562-1566

M-100907 Aventis
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M-100907 is a highly selective 5-HT$_{2A}$ antagonist that is being developed by Aventis Pharmaceuticals, formerly Hoechst Marion Roussel (HMR), for the potential treatment of schizophrenia. M-100907 is in phase III trials for chronic schizophrenia [307936], [307942], [307940]. In August 1999, development was discontinued for acute schizophrenia (schizoaffective disorder) on the basis of poor results [335083].

M-100907 is a potent antagonist in every putative animal behavioral model of schizophrenia that involves activation of 5-HT$_{2A}$ receptors [181713]. Interestingly, M-100907 is also active in animal models involving blockade of NMDA glutamatergic channel receptors, an effect known to resemble some behavioral symptoms of schizophrenia in man [390328].

M-100907 belongs to a series of piperidine derivatives, which were originally disclosed in the associated patent, EP-00208235. M-100907 is specifically claimed in a later patent, EP-00531410. This patent describes superior in vivo potency for M-100907 and its claims include the use of M-100907 for the treatment of thromboembolic disorders. The use of M-100907 for the treatment of various developmental neurological disorders such as autism and attention deficit hyperactivity disorder is disclosed in WO-09956750.

In 1996, this product was designated one of HMR's nine top priority products, serving an unmet medical need and addressing a potential market in excess of US $500 million per year [221118]. In January 1999, BT Alex Brown predicted sales of US $30 million in 2000 rising to US $220 million in 2002 [318220]. In April 1999, ABN Amro predicted annual sales of DM 50 million in 2000, rising to DM 150 million in 2002 [328676].

Originator Aventis Pharmaceuticals Inc

Status Phase 3 Clinical

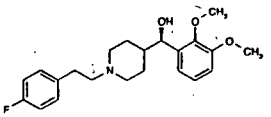
Indication Psychosis, Schizoaffective disorder, Schizophrenia

Action 5-HT$_{2A}$ antagonist

Synonyms MDL-100907, MDL-101860, MDL-28161, MDL-100151, MDL-105725, MDL-100009

CAS 4-Piperidinemethanol, α-(2,3-dimethoxyphenyl)-1-[2-(4-fluorophenyl)ethyl]-, (R)-
Registry No: 139290-65-6
Note: M-100907

CAS 4-Piperidinemethanol, 1-[2-(4-fluorophenyl)ethyl]- α-(3-hydroxy-2-methoxyphenyl)-, (αR)-
Registry No(s): 189192-18-5
Note: MDL-105725 - active metabolite



Introduction

For over 35 years, derivatives of chlorpromazine (phenothiazines) and haloperidol (butyrophenones) have been used successfully to treat psychotic behaviors, including schizophrenia. The exact mechanism of action of these antipsychotic agents remains to be elucidated, and many hypotheses have been proposed and tested in animal models. To date, the only reliable predictor of antipsychotic activity is the ability of an agent to inhibit the dopamine D$_2$ receptor [390342]. Unfortunately, this activity also correlates with incidences of extrapyramidal side effects (EPS) in man. With the observation that atypical antipsychotic agents also bind more potently to the 5-HT$_{2A}$ receptor, particularly *in vivo* [200641], it was suggested that this would lead to a lower propensity for causing EPS in man [1857]. This hypothesis is refuted by the fact that neither ketanserin nor ritanserin (Janssen Pharmaceutica NV) were able to reverse haloperidol-induced catalepsy in rats [390327], [390334], nor were schizophrenic patients free from experiencing EPS while taking olanzapine (Zyprexa; Eli Lilly & Co) or risperidone (Risperdal Janssen Pharmaceutica NV) in doses that caused high dopamine D$_2$ receptor occupancy and concomitant high 5-HT$_{2A}$ receptor occupancy [390321]. However, the idea that 5-HT$_{2A}$ receptor antagonism alone could convey antipsychotic activity [352899], perhaps through glutamate-mediated control of dopamine release [353639], [378994], was born [181713]. A definitive answer to this question requires an agent that selectively blocks the 5-HT$_{2A}$ receptor without inhibiting other neurotransmitter receptors. M-100907 is such an agent [390339].

Synthesis and SAR

The racemic desfluoro analog of M-100907 (MDL-26508) was synthesized in 1984 by Albert Carr and Norbert Wiech at Aventis (previously known as Merrell-Dow, then Hoechst-Marion Roussel [350762]) in Cincinnati (US-05169096). Two different routes for producing racemic M-100907 (MDL-100151) have been reported: (i) Ethyl isonipecotate is *N*-alkylated with 4-fluorophenethyl bromide and the product is treated with *N,O*-dimethylhydroxylamine and ethylmagnesium bromide [390318]. Reaction with the lithium salt of veratrole and reduction with sodium borohydride gives MDL-100151; (ii) isonipecotic acid is alkylated with di-tert-butyl dicarbonate and the resulting product is condensed with *N,O*-dimethylhydroxylamine to give the BOC-protected 4-(*N*-methoxy-*N*-methylcarboxamido)-1-piperidine. Reaction with the lithium salt of veratrole as